

AM

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification⁵ : C07C 43/215, A61K 31/09 C07C 43/225, 43/23, 69/157 C07C 49/84, 205/35, 217/58	A1	(11) International Publication Number: WO 93/23357 (43) International Publication Date: 25 November 1993 (25.11.93)
(21) International Application Number: PCT/US93/04807 (22) International Filing Date: 20 May 1993 (20.05.93) (30) Priority data: 887,725 21 May 1992 (21.05.92) US (71) Applicant: RESEARCH CORPORATION TECHNOLOGIES, INC. [US/US]; 101 N. Wilmot Road, Suite 600, Tucson, AZ 85711-3335 (US). (72) Inventors: CUSHMAN, Mark, S. ; 1715 Maywood Drive, West Lafayette, IN 47906 (US). HAMEL, Ernest ; 5200 Benton Avenue, Bethesda, MD 20892 (US). (74) Agent: SCOTT, Anthony, C.; Scully, Scott, Murphy & Presser, 400 Garden City Plaza, Garden City, NY 11530 (US).	(81) Designated States: AU, CA, JP, KR, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>With amended claims.</i> Date of publication of the amended claims: 6 January 1994 (06.01.94)	
(54) Title: STILBENE DERIVATIVES AS ANTICANCER AGENTS (57) Abstract <p>The present invention relates to stilbene derivatives which possess utility as anti-cancer agents. The compounds can be used to treat cancers which are susceptible to treatment therewith, and can be utilized in a method of treating such cancers. Pharmaceutical compositions containing the compounds are disclosed. Three preferred compounds among those disclosed are (Z)-1-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene, (Z)-1-(4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)ethene, and 4-methyl-3',4',5'-trimethoxybenzylamine hydrochloride.</p>		

Best Available Copy

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NE	Niger
BE	Belgium	GN	Guinea	NL	Netherlands
BF	Burkina Faso	GR	Greece	NO	Norway
BG	Bulgaria	HU	Hungary	NZ	New Zealand
BJ	Benin	IE	Ireland	PL	Poland
BR	Brazil	IT	Italy	PT	Portugal
BY	Belarus	JP	Japan	RO	Romania
CA	Canada	KP	Democratic People's Republic of Korea	RU	Russian Federation
CF	Central African Republic	KR	Republic of Korea	SD	Sudan
CG	Congo	KZ	Kazakhstan	SE	Sweden
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovak Republic
CM	Cameroon	LU	Luxembourg	SN	Senegal
CN	China	LV	Latvia	TD	Chad
CS	Czechoslovakia	MC	Monaco	TG	Togo
CZ	Czech Republic	MG	Madagascar	UA	Ukraine
DE	Germany	ML	Mali	US	United States of America
DK	Denmark	MN	Mongolia	UZ	Uzbekistan
ES	Spain			VN	Viet Nam
FI	Finland				

AMENDED CLAIMS

[received by the International Bureau on 18 November 1993 (18.11.93);
original claims 1-205 replaced by new claims 1-46 (12 pages)]

1

1. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound having the formula:

5



and pharmaceutically acceptable salts thereof, wherein:

Ar and Ar₁ are independently aryl or heteroaryl; and Ar may be mono, di, tri, or tetrasubstituted with R' and Ar₁ may be mono, di, tri, or tetrasubstituted with R'';

X is $\begin{array}{c} -C- \\ || \\ O \end{array}$, $-NH-CH_2-$, $-CH_2NH-$, $-NH-C-$, $-C-NH-$, $\begin{array}{c} || \\ O \end{array}$, $\begin{array}{c} || \\ O \end{array}$,
15 $-(Y_2)(Y_3)C-C(Z_2)(Z_3)-$ or cis or trans ethylene radical of the formula $-(Y_1)C=C(Z_1)$, CH₂, or CHOH;

Y₁, Y₂, Y₃, Z₁, Z₂ and Z₃ are independently hydrogen, lower alkyl, lower alkoxy, carboxy, lower carbalkoxy, COONR₁₃R₁₄, cyano, or COOQNR₁₅R₁₆;

20 R₁₃, R₁₄, R₁₅ and R₁₆ are independently hydrogen or lower alkyl;

Q is lower alkylene;

each R' may be the same or different and consists of R₁, R₂, R₃ and R₄, and each R'' may be the same or different and consists of R₅, R₆, R₇ and R₈;

25 R₁, R₂, R₃, R₄, R₅, R₆, R₇ and R₈ are independently hydrogen, lower alkyl, halo, amino, lower alkylamino, diloweralkylamino, lower alkoxy, lower arylalkoxy, cyano, aryloxy, mercapto, lower alkyl thio, amino lower alkyl, carboxy, carbolower alkoxy, CONHR₉, NHCO(R₉), lower alkanoyl, nitro, CF₃, lower alkyl
30 carbonyloxy, amino lower alkoxy, lower alkyl amino lower

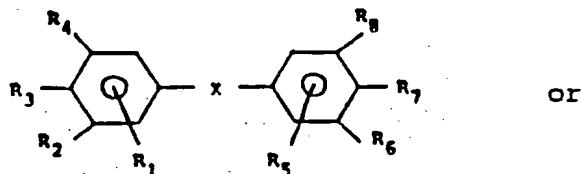
- 1 alkoxy, dilower alkylamino lower alkoxy, aminolower
alkylene oxycarbonyl, lower alkylamino loweralkyleneoxy
carbonyl, dilower alkylamino lower alkylene oxy
carbonyl, $\text{OSi}(\text{R}_{10}\text{R}_{11}\text{R}_{12})$ or $\text{Si}(\text{R}_{17})(\text{R}_{18})(\text{R}_{19})$ and at
5 least two or R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 and R_8 is
loweralkoxy;

R_9 is hydrogen or lower alkyl;

- 10 R_{10} , R_{11} , R_{17} , R_{18} and R_{19} are independently
lower alkyl; R_{12} is lower alkyl or lower alkoxy; and a
pharmaceutical carrier therefor.

2. The pharmaceutical composition according
to Claim 1 wherein Ar and Ar₁ are independently aryl.

- 15 3. The pharmaceutical composition according
to Claim 1 or 2 having the formula:



pharmaceutically acceptable salts thereof.

4. The pharmaceutical composition according to
any of Claims 1-3 wherein Y_2 and Z_2 are hydrogen.

- 25 5. The pharmaceutical composition according to
any of Claims 1-4, wherein Y_3 and Z_3 are independently
hydrogen, cyano or lower carbalkoxy.

6. The pharmaceutical composition according to
any of Claims 1-5, wherein Y_3 is hydrogen or cyano and
30 Z_3 is hydrogen, cyano or lower carbalkoxy.

7. The pharmaceutical composition according to
any of Claims 1-6, wherein Z_3 and Y_3 are hydrogen.

1 8.. The pharmaceutical composition according to
any of Claims 1-3 wherein at least one of Y_1 and Z_1 is
hydrogen.

5 9. The pharmaceutical composition of any of
Claims 1-3 or 8 wherein Y_1 is COOH, COOMe, CONHMe,
COONHEt, COO(CH₂)NEt₂, COO(CH₂)₂NMe₂ or hydrogen and Z_1
is hydrogen or COOH.

10 10. The pharmaceutical composition according
to any of claims 1-3 or 8-9 where X is cis or trans
CH=CH.

15 11. The pharmaceutical composition according
to any of Claims 1-10 wherein R_5 , R_6 , R_7 and R_8 are
independently hydrogen, lower alkoxy, thio alkyl, lower
alkyl, amino, lower alkylamino, diloweralkylamino,
loweralkyl carbonyloxy, aminoalkoxy, lower alkylamino
carbonyloxy or dilower alkylamino carbonyloxy.

20 12. The pharmaceutical composition according
to any of Claims 1-11 wherein R_6 , R_7 and R_8 are
independently hydrogen, lower alkoxy, halo, amino, lower
alkylamino, dilower alkylamino, lower alkyl thio or
lower alkyl.

25 13. The pharmaceutical composition according
to any of Claims 1-12 wherein R_1 , R_2 and R_4 are
independently hydrogen lower alkyl or lower alkoxy;

R_3 is hydrogen, lower alkyl, lower alkoxy,
arylalkoxy, loweralkyl carbonyloxy or OSi(R_{10} R_{11} R_{12});

R_5 is hydrogen, lower alkyl, halo or lower
alkoxy;

30 R_6 and R_8 are independently hydrogen, lower
alkyl or lower alkoxy;

R_7 is hydrogen, lower alkoxy, lower alkyl,
halo, lower alkyl carbonyloxy, OSi(R_{10} R_{11} R_{12}),

1 Si(R₁₇)(R₁₈)(R₁₉), amino, lower alkylamino, dilower

alkylamino, $\begin{array}{c} \text{O} \\ || \\ \text{NHC-R}_9 \end{array}$, diloweralkylamino lower alkoxy,
5 lower alkylthio, mercapto or nitro;

R₁₀, R₁₁, R₁₂, R₁₇, R₁₈ and R₁₉ are
independently lower alkyl; and

R₉ is lower alkyl or hydrogen.

14. The pharmaceutical composition according
10 to any of Claims 1-13 wherein R₇ is lower alkoxy,
hydrogen, halo, amino, lower alkylamino, dilower
alkylamino or lower alkyl thio.

15. The pharmaceutical composition according
to any of Claims 1-14 wherein R₇ is lower alkoxy, lower
15 alkylamino or diloweralkylamino.

16. The pharmaceutical composition according
to any of Claims 1-13 wherein R₂, R₃, R₄, R₆, R₇ and R₈
are independently lower alkoxy, hydrogen or lower alkyl.

17. The pharmaceutical composition according
20 to any of Claims 1-16 where at least three and at most
six of R₁, R₂, R₃, R₄, R₅, R₆, R₇ and R₈ are lower
alkoxy, wherein lower alkoxy is alkoxy having 1-4 carbon
atoms.

18. The pharmaceutical composition according
25 to any of Claims 1-17 wherein R₁ and R₅ are hydrogen.

19. The pharmaceutical composition, according
to any of Claims 1-18 wherein at least three of R₁, R₂,
R₃ and R₄ are lower alkoxy.

20. The pharmaceutical composition according
30 to any of Claims 1-19 wherein R₂, R₃ and R₄ are lower
alkoxy.

1 21. The pharmaceutical composition according
to any of Claims 1-20 wherein R_2 , R_3 and R_4 are lower
alkoxy and R_7 is lower alkoxy.

22. The pharmaceutical composition according
5 to any of Claims 1-21 wherein X is $-\text{C}-$.



23. The pharmaceutical composition according
to any of Claims 1-21 wherein X is $-\text{CHOH}-$.

24. The pharmaceutical composition according
10 to any of Claims 1-21 wherein X is $-\text{NH}-\text{CH}_2$ or $-\text{CH}_2\text{NH}-$.

25. The pharmaceutical composition according
to any of Claims 1-21 wherein X is $-\text{NHC}-$ or $-\text{C}-\text{NH}-$.



26. The pharmaceutical composition according
15 to any of Claims 1-21 wherein X is $-(Y_2)(Y_3)\text{C}-\text{C}(Z_2)(Z_3)$.

27. The pharmaceutical composition according
to any of Claims 1-21 wherein X is cis or trans
 $(Y_1)\text{C}=\text{C}(Z_1)$.

28. The pharmaceutical composition according
20 to any of Claims 1-27 wherein

X is cis $\text{HC}=\text{CH}$, R_1 , R_5 , R_6 and R_7 are H and R_2 ,
 R_3 , R_4 and R_7 is methoxy;

X is cis $\text{CH}=\text{CH}$; R_1 , R_5 , R_7 and R_8 are H; R_2 ,
25 R_3 , R_4 and R_6 are OCH_3 ;

X is cis $\text{CH}=\text{CH}$; R_1 , R_6 and R_8 are H; R_5 is 2-
 Cl ; R_2 , R_3 , R_4 and R_7 are OCH_3 ;

X is cis $\text{CH}=\text{CH}$; R_1 , R_5 , R_6 and R_8 are H; R_7 is
 Cl and R_2 , R_3 and R_4 are OCH_3 ;

30 X is cis $\text{CH}=\text{CH}$; R_1 , R_5 , R_6 and R_8 are H; R_7 is
 Br , and R_2 , R_3 and R_4 are OCH_3 ;

1 X is cis CH=CH; R_1 , R_5 , R_6 and R_8 are H; R_7 is
NMe₂, and R_2 , R_3 , R_4 are OCH₃;

X is cis CH=CH; R_1 , R_5 , R_6 and R_8 are H; R_7 is
OEt, and R_2 , R_3 and R_4 are OCH₃;

5 X is cis CH=CH; R_1 , R_5 , R_6 and R_8 are H; R_7 is
OPr, and R_2 , R_3 and R_4 are OCH₃;

X is cis CH=CH; R_1 , R_5 , R_6 and R_8 are H; R_7 is
SMe, and R_2 , R_3 and R_4 are OCH₃;

X is cis CH=CH; R_1 , R_5 , R_6 and R_8 are H; R_7 is
10 Me, and R_2 , R_3 and R_4 are OCH₃;

X is cis CH=CH; R_1 , R_5 , R_6 and R_8 are H; R_7 is
Et, and R_2 , R_3 and R_4 are OCH₃;

X is cis CH=CH; R_1 , R_5 , R_6 and R_8 are H; R_7 is
iPr, and R_2 , R_3 and R_4 are OCH₃;

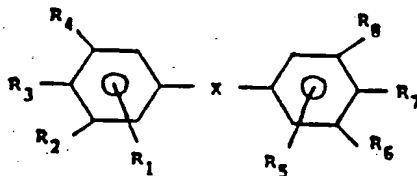
15 X is CH₂CH₂; R_1 , R_5 , R_6 and R_8 are H; R_2 , R_3 ,
 R_4 and R_7 are OCH₃; or

X is CHNH, R_1 , R_5 , R_6 and R_8 are H and R_2 , R_3 ,
 R_4 and R_7 are OCH₃.

29. A method for treating cancer in an animal
20 which comprises administering to said animal in need of
such treatment an anti-cancer effective amount of a
composition according to any of Claims 1-28.

30. The compound having the formula:

25



30

35

1 wherein:

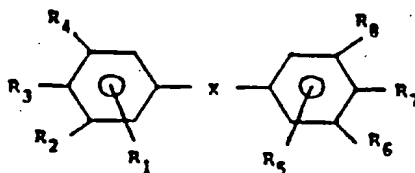
X is $-\text{NH}-\text{CH}_2-$, $-\text{CH}_2\text{NH}-$, $-\overset{\text{O}}{\parallel}\text{C}-\text{NH}-$ or $-\text{NHC}-\overset{\text{O}}{\parallel}$;

5 R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 and R_8 are independently hydrogen, lower alkyl, halo, amino, lower alkylamino, diloweralkylamino, lower alkoxy, lower arylalkoxy, cyano, aryloxy, mercapto, lower alkyl thio, amino lower alkyl, carboxy, carbolower alkoxy, CONHR_9 , $\text{NHCO}(\text{R}_9)$, lower alkanoyl, nitro, CF_3 , lower alkyl
 10 carbonyloxy, amino lower alkoxy, lower alkyl amino lower alkoxy, dilower alkylamino lower alkoxy, amino lower alkylene oxycarbonyl, lower alkylamino loweralkyleneoxy carbonyl, dilower alkylamino lower alkylene oxy carbonyl, $\text{OSi}(\text{R}_{10}\text{R}_{11}\text{R}_{12})$ or
 15 $\text{Si}(\text{R}_{17})(\text{R}_{18})(\text{R}_{19})$ and at least two of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 and R_8 is loweralkoxy;

R_9 is hydrogen or lower alkyl;

R_{10} , R_{11} , R_{12} , R_{17} , R_{18} and R_{19} are independently lower alkyl.

20 31. The compound having the formula



25

wherein X is a cis ethylene radical of the formula
 $-(\text{Y}_1)\text{C}=\text{C}(\text{Z}_1)-$;

Y_1 and Z_1 are independently hydrogen, lower
 30 alkyl, lower alkoxy, carboxy, lower carbalkoxy,
 $\text{COONR}_{13}\text{R}_{14}$, cyano, or $\text{COOQNR}_{15}\text{R}_{16}$;

35

- 1 R_{13} , R_{14} , R_{15} and R_{16} are independently
hydrogen or lower alkyl;
 Q is lower alkylene;
 R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 and R_8 are
5 independently hydrogen, lower alkyl, halo, amino, lower
alkylamino, diloweralkylamino, lower alkoxy, lower
arylalkoxy, cyano, aryloxy, mercapto, lower alkyl thio,
amino lower alkyl, carboxy, carbolower alkoxy, $CONHR_9$,
 $NHCO(R_9)$, lower alkanoyl, nitro, CF_3 , lower alkyl
10 carbonyloxy, amino lower alkoxy, lower alkyl amino lower
alkoxy, dilower alkylamino lower alkoxy,
amino lower alkylene oxycarbonyl, lower alkylamino
loweralkyleneoxy carbonyl, dilower alkylamino lower
alkylene oxy carbonyl, $OSi(R_{10}R_{11}R_{12})$ or
15 $Si(R_{17})(R_{18})(R_{19})$ and at least two of R_1 , R_2 , R_3 , R_4 ,
 R_5 , R_6 , R_7 and R_8 is loweralkoxy;
 R_9 is hydrogen or lower alkyl; and
 R_{10} , R_{11} , R_{12} , R_{17} , R_{18} and R_{19} are
independently lower alkyl.

20 32. The compound according to Claim 31 wherein
at least one of Y and Z is hydrogen.

33. The compound according to Claim 31 or 32,
wherein Y is $COOH$, $COOMe$, $CONHMe$, $COONHET$, $COO(CH_2)NMe_2$,
 $COO(CH_2)_2NMe_2$ or hydrogen and Z is hydrogen or $COOH$.

25 34. The compound according to any of Claims 31-
33 wherein X is $cis -HC=CH-$;

R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 and R_8 are
independently hydrogen, lower alkyl, halo, amino, lower
alkylamino, diloweralkylamino, lower alkoxy, lower
30 arylalkoxy, cyano, aryloxy, mercapto, lower alkyl thio,
amino lower alkyl, carboxy, carbolower alkoxy, $CONHR_9$,
 $NHCO(R_9)$, lower alkanoyl, nitro, CF_3 , lower alkyl

- 1 carbonyloxy, amino lower alkoxy, lower alkyl amino lower
 alkoxy, dilower alkylamino lower alkoxy,
 amino lower alkylene oxycarbonyl, lower alkylamino
 loweralkyleneoxy carbonyl, dilower alkylamino lower
 5 alkylene oxy carbonyl, $\text{OSi}(\text{R}_{10}\text{R}_{11}\text{R}_{12})$ or
 $\text{Si}(\text{R}_{17})(\text{R}_{18})(\text{R}_{19})$ and at least two of $\text{R}_1, \text{R}_2, \text{R}_3, \text{R}_4,$
 $\text{R}_5, \text{R}_6, \text{R}_7$ and R_8 is loweralkoxy;

R_9 is hydrogen or lower alkyl; and

$\text{R}_{10}, \text{R}_{11}, \text{R}_{12}, \text{R}_{17}, \text{R}_{18}$ and R_{19} are

- 10 independently lower alkyl.

35. The compound according to any of Claims 31-
 34 wherein at least three and at most six of $\text{R}_1, \text{R}_2, \text{R}_3,$
 $\text{R}_4, \text{R}_5, \text{R}_6, \text{R}_7$ or R_8 is lower alkoxy.

36. The compound according to any of Claims 31-
 15 35 wherein three of $\text{R}_1, \text{R}_2, \text{R}_3$ or R_4 are lower alkoxy.

37. The compound according to any of Claims 31-
 36 wherein R_1, R_2 and R_4 are independently hydrogen or
 lower alkoxy;

- 20 R_3 is hydrogen, lower alkoxy, arylalkoxy,
 loweralkyl carbonyloxy or $\text{OSi}(\text{R}_{10}\text{R}_{11}\text{R}_{12})$;

R_5 is hydrogen, halo or lower alkoxy;

R_6 and R_8 are independently hydrogen or lower
 alkoxy;

- 25 R_7 is hydrogen, lower alkoxy, lower alkyl,
 halo, lower alkyl carbonyloxy, $\text{OSi}(\text{R}_{10}\text{R}_{11}\text{R}_{12}),$
 $\text{Si}(\text{R}_{17})(\text{R}_{18})(\text{R}_{19}),$ amino,

- lower alkylamino, dilower alkylamino, $\text{NHC}-\text{R}_9,$
 diloweralkyl-amino lower alkoxy, lower alkylthio,
 30 mercapto or nitro;

$\text{R}_{10}, \text{R}_{11}, \text{R}_{12}, \text{R}_{17}, \text{R}_{18}$ and R_{19} are
 independently lower alkyl; and

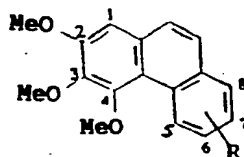
1 R_9 is lower alkyl or hydrogen.

38. The compound according to any of Claims
31-37 wherein R_1 and R_5 are hydrogen.

39. The compound according to any of Claims
5 31-38 wherein R_2 , R_3 , R_4 , R_6 , R_7 , and R_8 are
independently hydrogen or lower alkoxy

40. The compound according to any of Claims
31-39 wherein R_2 , R_3 and R_4 are lower alkoxy.

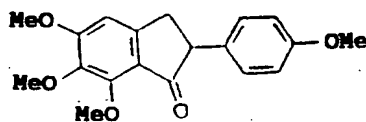
41. The compound selected from the group
10 consisting of:



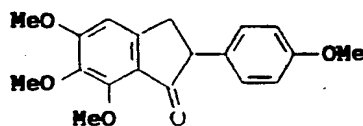
15

wherein R is C_{1-4} lower alkoxy;

20



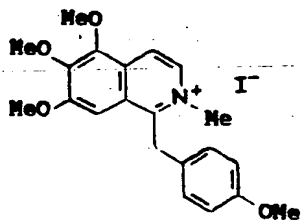
25



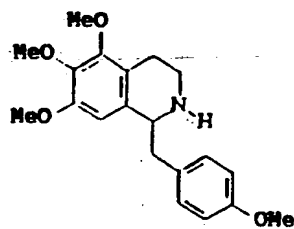
30

35

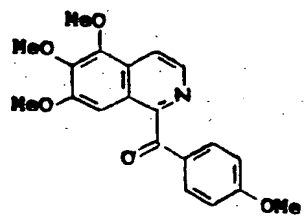
1



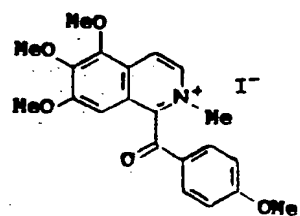
5



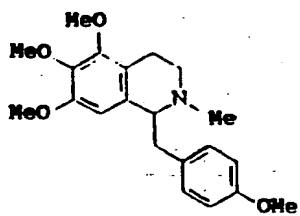
10



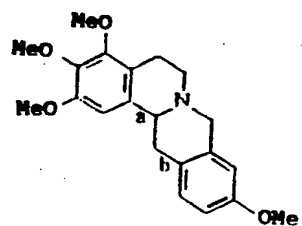
15



20

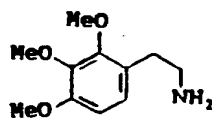


25



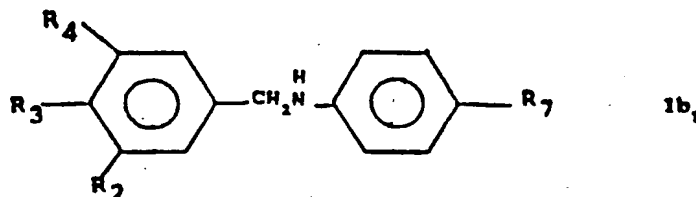
; and

30



35

- 1 42. The compound according to Claim 37 wherein
the compound has the formula:



- 10 wherein R₂, R₃ and R₄ are lower alkoxy and R₇ is
hydrogen, lower alkyl, halo, thioloweralkyl, lower
alkoxy, CF₃, lower alkanoyl, formyl, carboxy,
carbolloweralkoxy, nitro, SO₃H or cyano.
- 15 43. The compound of Claim 42 wherein R₇ is
hydrogen, trifluoro-methyl, lower alkyl, halo, thio-
loweralkyl or lower alkoxy.
- 20 44. The compound according to any of Claims
42-43 which is 4-methyl-N-(3,4,5-
trimethoxybenzyl)aniline,
4-ethyl-N-(3,4,5-trimethoxybenzyl)aniline, or 4-methoxy-
N-(3,4,5-trimethoxybenzyl)aniline or pharmaceutically
acceptable salts thereof.
- 25 45. A method for treating cancer in an animal
which comprises administering to said animal in need of
such treatment an anti-cancer effective amount of a
compound according to any of Claims 31-44.
- 30 46. A pharmaceutical composition comprising a
pharmaceutically effective amount of a compound
according to any of Claims 31-44 and a pharmaceutical
carrier therefor.

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☒ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☒ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.